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Consensus Validation of the POSAMINO (POtentially Serious Alcohol Medication INteractions in Older adults) Criteria

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Abstract:

Objectives: Older adults are particularly vulnerable to adverse effects from concurrent alcohol and medication use. However, there is limited evidence regarding the prevalence of these adverse outcomes among older adults and there is a lack of consensus regarding what constitutes an alcohol-interactive medicine. The objective of this study was to develop an explicit list of potentially serious alcohol-medication interactions for use in older adults.

Design: Following a systematic review, review of drug compendia and clinical guidance documents, a two-round Delphi consensus method was conducted.

Setting: Ireland and the United Kingdom (UK), primary care and hospital setting.

Participants: The Project Steering Group developed a list of potentially serious alcohol-medication interactions. The Delphi panel consisted of 19 healthcare professionals (general practitioners (GPs), geriatricians, hospital and community pharmacists, clinical pharmacologists and pharmacists and physicians specialising in substance misuse).

Results: An inventory of 52 potentially serious alcohol-medication interactions was developed by the Project Steering Group. British National Formulary (BNF) black dot warnings (n=8) were included in the final criteria as they represent 'potentially serious' interactions. The remaining 44 criteria underwent a two-round Delphi process. In the first round, thirteen criteria were accepted into the POSAMINO criteria. Consensus was not reached on the remaining 31 criteria; nine were removed, and eight additional criteria were included following a review of panellist comments. The remaining 30 criteria went to round-two, with 17 criteria reaching consensus, providing a final list of 38 potentially serious alcohol-medication interactions; central nervous system (n=15), cardiovascular system (n=9), endocrine system (n=5), musculoskeletal system (n=3), infections (n=3), malignant disease & immunosuppression (n=2) and respiratory system (n=1).

Conclusions: POSAMINO is the first set of explicit potentially serious alcohol-medication interactions for use in older adults. These criteria will facilitate the risk stratification of older adults at the point of prescribing.

Strengths and limitations of this study:

- The potentially serious alcohol-medication interactions for use in older adults (POSAMINO) criteria were developed in a robust fashion, using a two-step process involving a systematic review and two-round Delphi process.
- The Delphi consensus technique utilised in this study is flexible and enabled communication from a diverse group of healthcare professionals from both the United Kingdom and Ireland.
- The final criteria will need to be further validated prospectively to quantify the magnitude of risk posed for each criterion for adverse outcomes in older adults.
- Once validated, these criteria have the potential to inform medical decision making and enable healthcare professionals to risk stratify older adults at the point of prescribing and prioritise alcohol screening and brief interventions in high-risk groups.

Background

Population demographics are changing globally, with the proportion and age of the older population continuing to increase. (1) While alcohol consumption tends to decline in older age, recent evidence suggests that drinking occasions tend to become more frequent among older adults. (2) There is also evidence of a cohort effect with successive birth cohorts reporting an increase in alcohol consumption among all age groups, including older adults. (3) Ageing is associated with a variety of physiological changes which may place older adults at an increased risk of alcohol-related health problems. (4, 5) In fact, older adults experience a disproportionate burden of alcohol related-harm; in England between 2009 and 2010, adults aged ≥ 65 years accounted for approximately 44% (461,400) of alcohol-related hospital admissions yet comprised of only 17% of the population.(5) Alcohol-related deaths were also highest among those aged 55 to 74 years. (5)

Polypharmacy is also increasing in older adults. (6) For example, approximately 60% of Irish adults aged ≥ 65 years reported taking five or more medicines in 2012. (6) Certain medicines have the potential to interact with alcohol increasing the risk of medical complications such as hypoglycaemia, hypotension, sedation, gastrointestinal bleeds and liver damage. (7, 8) Alcohol interactive (AI) medicines may interact with alcohol by altering the metabolism (pharmacokinetic) or effects (pharmacodynamic) of alcohol and/or the medication. (8) Interactions may occur with any alcohol or follow a dose response, with the risk or severity of an interaction increasing with increasing levels of alcohol consumption. (7)

While a number of studies have investigated the concurrent use of alcohol and medicines with potential to interact with alcohol among older adults, (9-28) there is a lack of consensus regarding what constitutes an AI medication across studies. Several studies focussed on a wide range of medications, using different drug compendia to identify medications as alcohol interactive, thus leading to a lack of consistency in the inclusion of medicines as alcohol interactive. (9-12, 16, 19, 21-23) Other studies focussed on psychotropic medications alone, specifically sedatives and hypnotics. (13, 15, 17, 18, 20, 24, 26, 28)

While there appears to be a high propensity for alcohol-medication interactions among community dwelling older adults, with between one-in-five to one-in-three older adults potentially susceptible to alcohol-

medication interactions, (11, 12, 23) no study to date has examined longitudinal associations of concurrent use with adverse outcomes. An evidence based list of medications which have a significant risk of harm to older patients when combined with alcohol would be useful in a clinical setting, allowing for the identification of older adults whose alcohol consumption places them at increased risk and who would benefit from a preventative intervention. Therefore, the aim of this study is to derive the first set of explicit potentially serious alcohol-medication interactions in older adults.

Methods

Study design

A Delphi consensus technique was used to develop the list of potentially serious alcohol-medication interactions in older adults. The Delphi method allows a consensus opinion to be reached amongst a panel of experts through an iterative process of questionnaires. (29) Ethics approval for this study was obtained from the Royal College of Surgeons in Ireland (Reference Number REC1097).

Compilation of initial list of potentially serious alcohol-medication interactions

An extensive list of medications with potential to interact with alcohol was identified by the Project Steering Group following a comprehensive systematic search using MEDLINE (PubMed), Embase, Scopus and Web of Science databases. A combination of the following keywords and MeSH terms were used: "ethanol", "alcohol", "drug interactions", "drug alcohol interaction" and "aged". This search was supplemented by a search in Google Scholar and by hand searching references of retrieved articles. The search was restricted to English language articles and articles published since January 1990. Furthermore, the British National Formulary (BNF), Stockley's Drug Interactions and Martindale Complete Drug Reference drug compendia were also searched (30-32). Additional documents such as clinical guidance documents (33) and previous reviews (7, 8) were also accessed. Information extracted included: medication name/class, potential adverse outcome(s), whether an interaction is likely to occur with any alcohol consumption or with heavy consumption using national low risk drinking guidelines (34, 35) and, if reported, evidence supporting the interaction. The list of medications was organised according to the BNF physiological classification system. There was considerable heterogeneity across reference sources in terms of identifying medications as having potential to interact with alcohol, with no age specific information for interactions. Furthermore, there were inconsistencies in relation to the quantity of concurrent alcohol consumption that should be avoided. For example, the Martindale mentioned that alcohol combined with NSAIDs may increase the risk of gastrointestinal bleeds with no mention of alcohol consumption patterns, Stockley's described that both NSAIDs and excessive alcohol use carry the risk of gastrointestinal adverse effects, while NSAIDs and alcohol were not included as an interaction in the BNF. For the next step, the Project Steering Group

reviewed and assessed each medication or drug class. Using the definition of "necessary to avoid" previously described by Dreischulte et al. (36), it was considered necessary to avoid concurrent alcohol with a specific medication if, in an average older adult concurrent use of alcohol with this medication would be considered unsafe because (a) there is sufficient evidence that the patient is likely to be harmed, and (b) the likely harm to the patient is large enough to be clinically significant.

Drugs were excluded for the following reasons: their interaction with alcohol was not considered serious; the medication is not licensed for use in older adults; the medication is only administered in a hospital environment (for example Trabectedin), interaction with alcohol may only occur during alcohol withdrawal or has been withdrawn from the market in the UK or Ireland. Following these exclusions a truncated list was further reviewed by the Project Steering Group by a consensus discussion. In this process the Project Steering Group agreed, that BNF black dot warnings would be included in the final list as these are potentially serious interactions and concomitant administration of alcohol should be avoided. (30) Furthermore, the amount of alcohol to be avoided with each medication class was defined through group discussion, based on both the evidence available and the members' own clinical experience. Additionally, it was agreed that the following adverse outcomes associated with concurrent use were defined using clinical guidance documents and reviews to ensure clarity among all participants: orthostatic hypotension (37), hypoglycaemia (38) and lactic acidosis (39).

Selection of the Delphi panel

A total of 51 experts from the Republic of Ireland and United Kingdom, were invited (via e-mail or letter) to participate as part of the Delphi consensus panel. Participants were identified by the Project Steering Group on the basis of their clinical expertise or knowledge of alcohol-medication interactions or care of older persons. Reasons for non-participation were not required; however in some instances they were provided, they included time commitments and lack of clinical knowledge of alcohol-medication interactions. In total, 19 participants (37%) agreed to participate and written consent was received from all participants before the study. The panel consisted of general practitioners (GPs) (n=5), geriatricians (n=3), hospital pharmacists with expertise in care of older adults (n=3), community pharmacists (n=3), clinical pharmacologists (n=2),

clinical pharmacists specialising in substance misuse (n=2) and a physician specialising in substance misuse (n=1).

The Delphi validation technique and process

An online questionnaire was piloted by two pharmacists and two GPs, to identify any potential problems and to approximate the completion time for the survey. Following amendments, the 19 participants were sent a link to the online POSAMINO questionnaire (via SurveyGizmo®) in March 2016. Participants were given four weeks to complete the online questionnaire and all participants were sent a reminder email after 2 weeks to encourage participation. The questionnaire was both anonymous and confidential.

The quantity of alcohol per standard drink (SD) (10 grammes alcohol in Ireland) or unit (8 grammes alcohol in the United Kingdom), was defined at the beginning of the survey. As some interactions are listed with any alcohol consumption and others with 'heavy' consumption, we provided definitions of both at the beginning of the questionnaire. Any alcohol consumption was defined as ≥1 SD of alcohol in Ireland or ≥1 unit of alcohol in the UK, with heavy consumption defined according to Irish and UK National low risk drinking guidelines. (34, 35) The panel were instructed to evaluate each potential interaction listed according to the "necessary to avoid" framework described above. (36) Medications were categorised according to the BNF physiological classification system. Each statement was presented in the same format stating: It is necessary to avoid [quantity of alcohol] (any or heavy) with [medications/ drug class], followed by a brief rationale for the statement. For example: *It is necessary to avoid: Any alcohol consumption with first generation anti-histamines (for example promethazine). (Rationale: Concurrent alcohol consumption with first generation anti-histamines can increase the risk of sedation).*

Participants were asked to rate their agreement with each statement, using a 5-point Likert scale (1-strongly disagree to 5-strongly agree) along with any additional comments, or suggestions for additional medicines to be included.

After each round, the median and interquartile ranges (IQR) were calculated for each statement. Consistent with previous Delphi consensus studies, the consensus level required for a statement to be retained was defined *a priori* as a median of 4 or 5 with a lower quartile value of ≥ 4. (40) If a statement had an upper

quartile value of ≤ 2, this indicated there was general disagreement with the statement between panel members, and the statement was rejected. If group consensus was not reached, the criteria were reviewed by the Project Steering Group and were removed based on comments or revised and included in the second questionnaire. In the second questionnaire, panellists were provided with links to the most recent evidence relating to each of the alcohol-medication interactions, to help facilitate their decisions due to uncertainty in round 1. As with round one, the median response and IQR were calculated and evaluated by the Project Steering Group using the same thresholds to determine consensus between the panel members. If consensus was not reached following the second round, the statement was rejected. Statistical analysis was performed using STATA version 13 and Microsoft Excel 2010.

Results

Following an initial review of the literature, Anatomical Therapeutic Chemical (ATC) codes for a total of 364 AI medicines were extracted by the Project Steering Group. Medicines were classified according to drug classes and organised according to BNF physiological classification systems. From this list, a total of 63 statements were initially compiled based on the 'necessary to avoid' framework. (36) Following group discussions, 11 statements were removed/updated or merged together, based on the steering groups clinical knowledge or experience with medicines. For example, the steering group decided to no longer classify benzodiazepines according to the duration of action, as both long acting and short acting have the potential to interact with alcohol. Furthermore, a total of eight BNF black dot warnings were included in the final criteria as they represent potentially serious interactions.

All 19 panel members completed the round one questionnaire, in which forty-four statements were presented. Consensus was reached on 13 statements, with no statements rejected **(Table 1)**. Thirty one statements were reviewed by the steering group, with nine statements removed based on comments from the panel, if the interaction was not relevant to older adults or the interaction was not of clinical significance for example: heavy alcohol consumption with vitamin A preparations. Furthermore, eight new statements were included in round two based on comments from panellists at the first round.

A total of 18 out of the 19 recruited participants completed the round two questionnaire. Of the 30 statements included in the second questionnaire, consensus was reached for 17 statements. The remaining 13 statements were rejected as no consensus was reached. In total, consensus was reached for 30 potentially serious drug alcohol interactions in older adults, with the inclusion of BNF black dot warnings the final list was 38 statements.

INSERT TABLE 1 HERE

This final 38 item POSAMINO criteria **(Table 2)** were organised over the following physiological systems: Central nervous system (n=15), cardiovascular system **(**n=9), endocrine system (n=5), musculoskeletal system (n=3), infections (n=3), malignant disease and immunosuppression (n=2) and respiratory system (n=1).

INSERT TABLE 2 HERE

Discussion

While older adults experience a disproportionate burden of alcohol related harm, (5) research suggests that healthcare professionals are less likely to discuss alcohol consumption with older adults. (41, 42) Flagging older adults at the point of prescribing an alcohol-interactive medication may facilitate targeted screening and interventions to help reduce harm. Despite the high propensity for alcohol-medication interactions among community dwelling older adults, (9-28) there is still a lack of consensus regarding what constitutes an AI medication.

This study reports the development of a set of 38 explicit criteria, POSAMINO, for identifying older adults at risk of potentially serious alcohol-medication interactions. The development of these criteria is important for several reasons. In the absence of an explicit list of alcohol-interactive medications, multiple drug reference sources have been used in previous studies leading to a lack of consistency in the inclusion of medications across studies, (11, 12, 19, 22, 23) which may result in biased estimates of potential risk among older adults. Furthermore, some of these interactions may be theoretical with trivial clinical significance. Therefore, this study developed a consensus-based set of explicit criteria for potentially serious alcohol-medication interactions in older adults rather than an exhaustive list of medications with potential to interact with alcohol.

Principle findings

The final POSAMINO criteria consist of seven different drug classes. Central nervous system (CNS) medicines represent 40% of the criteria. Estimates from our previous study indicate that approximately one in five older Irish adults are exposed to CNS agents, with over half of patients using CNS agents reporting concurrent alcohol consumption. (12) Nine of the final 38 criteria concern cardiovascular agents, another widely used drug class among aged adults. (12) There is also a high-risk of adverse effects associated with these agents, with anti-platelets, diuretics and anticoagulants identified as the most common drug classes involved in preventable drug-related admissions. (43) Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, paracetamol and gabapentin (used for neuropathic pain) were also included in the final POSAMINO criteria. (43) The prevalence of chronic pain increases with age and older adults may

consume alcohol to help cope and manage their pain. (45) This behaviour may also predispose older adults to adverse outcomes associated with concurrent use with analgesics (for example increased sedation, falls and gastrointestinal bleeds).

Clinical implications and future research

This study adds to a growing body of research investigating the concurrent use of alcohol and alcohol interactive medicines in older adults. Undoubtedly, adverse drug events (ADEs) represent a major burden on healthcare, with ADEs detected in 26.3% of patients aged ≥ 65 years admitted to an Irish hospital with acute illnesses. (44) The increasing use of multiple medications, (6) combined with an increased frequency of alcohol consumption (2) and age-related physiological changes, may predispose older adults to these adverse events. The significant burden of alcohol-related harm and mortality among older adults, (5) indicates a pressing need for future interventions to minimise risk. The final criteria developed from this study, will need to be further validated prospectively to quantify the magnitude of risk posed for each criterion for adverse outcomes in older adults. Once validated, these criteria have the potential to inform medical decision making and enable healthcare professionals to risk stratify older adults at the point of prescribing and prioritise alcohol screening and brief interventions in high-risk groups . This is essential, as older people have previously reported little knowledge about risks associated with the concurrent use of alcohol and medications. (45)

Strengths and Limitations

The criteria were developed in a robust fashion, using a two-step process involving a systematic review and two-round Delphi process. The Delphi technique is flexible and for this study enabled communication from a group of nineteen healthcare professionals from both the United Kingdom and Ireland. Eighteen of the 19 participants completed the two rounds, with participants providing numerous comments and suggestions in both rounds. Similar to previous studies, participants remained anonymous and were not provided with feedback following the first round in order to remove the risk of potential bias. (40)

Inevitably, there were limitations to this Delphi study. With all Delphi studies, participants' judgements may be deemed subjective. In order to reduce this potential bias, a diverse group of healthcare professionals with

expertise or interest in the care of older adults were selected. With explicit criteria, there is also a need for regular updates and revision due to the availability of more up to date information after development. (46) The developed POSAMINO criteria do not apply to older adults diagnosed with an alcohol use disorder, as chronic heavy alcohol consumption can substantially increase the activity of the cytochrome P450 metabolising enzyme CYP2E1. (8) Finally, older adults may also experience chronic illnesses which affect the metabolism of both alcohol and medications. As a result, it is important that healthcare professionals also consider these comorbid diseases when assessing the risk for potential adverse outcomes. (47)

Conclusions

Using a systematic review and a two-round Delphi consensus method, we have developed the first set of explicit potentially serious alcohol-medication interactions (POSAMINO) for use in older adults. These criteria will allow for the risk stratification of older adults at the point of prescribing, and prioritise alcohol screening and brief alcohol interventions in high-risk groups.

Declarations:

Authors' contributions: AH, PG, CR, TF & GC (the project steering group) conceived and designed this study. AH & GC conducted initial literature search. AH communicated with Delphi participants. AH analysed the data after each round. All Project Steering Group members were involved in interpretation of the data. AH & GC drafted the manuscript. All co-authors revised the manuscript and have given the approval for publication.

Competing interests: The authors declare that they have no competing interests.

Ethics approval: Ethical approval for this study was approved by the Royal College of Surgeons in Ireland (RCSI) ethics committee (REC 1097).

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Data sharing statement: Additional data is available by request from the corresponding author.

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Table 1: Results from the 2-round Delphi process

	Potentially serious interactions as listed in the BNF	Round 1					Round 2					Final Criteria
Physiological System		**Total**	**Accept**	**Revise**	**Reject**	**Removal**	**New statements included**	**Total**	**Accept**	**Revise**	**Reject**	
Cardiovascular System	1	14	1	13	0	3	2	12	7	0	5	9
Respiratory System	0	1	1	0	0	0	0	0	0	0	0	1
Central Nervous System	4	12	6	6	0	1	5	10	5	0	5	15
Infections	2	5	0	5	0	3	0	2	1	0	1	3
Endocrine System	0	5	3	2	0	0	0	2	2	0	0	5
Obstetrics, Gynaecology, and Urinary Tract Disorders	0	2	0	2	0	1	1	2	0	0	2	0
Malignant Disease and Immunosuppression	1	1	0	1	0	0	0	1	1	0	0	2
Nutrition and Blood	0	1	0	1	0	1	0	0	0	0	0	0
Musculoskeletal System	0	3	2	1	0	0	0	1	1	0	0	3
Total	**8**	**44**	**13**	**31**	**0**	**9**	**8**	**30**	**17**	**0**	**13**	**38**

Table 2: Final POSAMINO Criteria (n=38)

CVS System

1. **Heavy alcohol consumption** with multiple anti-hypertensive combinations
   Rationale: Concurrent use of alcohol consumption and anti-hypertensives may increase the risk of orthostatic hypotension
2. **Heavy alcohol consumption** with warfarin (& phenindione)
   Rationale: Heavy episodic alcohol consumption is associated with an increased risk of major bleeds
3. **Heavy alcohol consumption** with regular use of low dose aspirin (75mg)
   Rationale: Heavy alcohol consumption combined with aspirin may cause a small increase in gastrointestinal blood loss
4. **Heavy alcohol consumption** with both regular and as required nitrates (e.g. glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate)
   Rationale: The combined haemodynamic effects of alcohol and nitrates, increases the risk of exaggerated hypotension.
5. **Heavy alcohol consumption** with the vasodilatory medication nicorandil
   Rationale: The combined haemodynamic effects of alcohol & nicorandil; increases the risk of exaggerated hypotension.
6. **Heavy alcohol consumption** with the combined use of both nitrates and vasodilator medication (e.g. nicorandil)
   Rationale: The combined haemodynamic effects of alcohol and nitrates, increases the risk of exaggerated hypotension.
7. **Heavy alcohol consumption** with diuretics (e.g. loop diuretics (furosemide), thiazide diuretics (bendroflumethiazide) & potassium sparing diuretics (amiloride))
   Rationale: The concurrent use of alcohol and anti-hypertensives may increase the risk of orthostatic hypotension.
8. **Heavy alcohol consumption** with alpha blockers (e.g. terazosin)
   Rationale: The concurrent use of alcohol and anti-hypertensives may increase the risk of orthostatic hypotension.
9. **Heavy alcohol consumption** with centrally acting anti-hypertensives (e.g. clonidine or methyldopa)
   Rationale: Alcohol consumption combined with centrally acting anti-hypertensives may increase the risk of sedation.

Respiratory System

1. **Any alcohol consumption** with first generation anti-histamines (e.g. promethazine)
   Rationale: Concurrent alcohol consumption with first generation anti-histamines can increase the risk of sedation

Central Nervous System

1. **Heavy alcohol consumption** with benzodiazepines (e.g.diazepam) and benzodiazepine related medications (e.g.zopiclone)
   Rationale: Alcohol consumption combined with benzodiazepines and benzodiazepine related medications may enhance CNS depressant effects
2. **Heavy alcohol consumption** combined with opioids
   Rationale: Alcohol consumption combined with opioids may enhance CNS depressant effects of alcohol
3. **Heavy alcohol consumption** with duloxetine
   Rationale: Heavy alcohol consumption combined with duloxetine may increase the risk of hepatotoxicity
4. **Heavy alcohol consumption** with all anti-psychotics
   Rationale: Alcohol consumption combined with antipsychotics may increase the risk of sedation
5. **Any alcohol consumption** with barbiturates
   Rationale: Alcohol consumption combined with barbiturates may increase the risk of sedation.
6. **Heavy alcohol consumption** with anti-epileptic drugs (AEDs)
   Rationale: Heavy alcohol consumption can increase the risk of seizures and sedation in patients taking AEDs.
7. **Any alcohol consumption** with tricyclic anti-depressants (TCAs)
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
8. **Any alcohol consumption** with tetracyclic antidepressants
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
9. **Any alcohol consumption** with mirtazapine
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
10. **Any alcohol consumption** with monoamine oxidase inhibitors (MAOIs)
    Rationale: A potentially life-threatening hypertensive reaction can develop in patients taking non-selective MAOIs who consume drinks rich in tyramine (e.g. wines, beers and non-alcoholic beers)
11. **Heavy alcohol consumption** with long term regular paracetamol use (e.g. 1g four times a day)
    Rationale: Heavy alcohol consumption may increase the risk of paracetamol hepatotoxicity especially if alcohol intake is abruptly stopped.
12. **Heavy alcohol consumption** with gabapentin (when used for neuropathic pain)
    Rationale: Alcohol combined with medications for neuropathic pain may increase the risk of sedation
13. **Heavy alcohol consumption** with pramipexole or amantadine
    Rationale: Alcohol may increase the risk of sedation
14. **Heavy alcohol consumption** with apomorphine

Rationale: *Alcohol combined with apomorphine may increase the risk of orthostatic hypotension*

15. **Heavy alcohol consumption** with levodopa (alone or in combination with carbidopa)
Rationale: Alcohol combined with levodopa (alone or in combination with carbidopa) may increase the risk of orthostatic hypotension.

Endocrine

1. **Heavy alcohol consumption** with insulin
Rationale: Alcohol consumption may enhance the hypoglycaemic effect of insulin.
2. **Heavy alcohol consumption** with metformin
Rationale: Heavy alcohol consumption combined with metformin may increase the risk of lactic acidosis
3. **Heavy alcohol consumption** with sulphonylureas
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics
4. **Heavy alcohol consumption** with meglitinides (e.g. nateglinide)
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics
5. **Heavy alcohol consumption** with thiazolidinediones (e.g. pioglitazone)
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics

Musculoskeletal and joint diseases

1. **Heavy alcohol consumption** with any nonsteroidal anti-inflammatory drugs NSAIDs (including COX-2 inhibitors)
Rationale: Heavy alcohol consumption and NSAID use carry an increased risk of gastrointestinal bleeds
2. **Heavy alcohol consumption** combined with methotrexate or leflunomide
Rationale: Heavy alcohol consumption combined with methotrexate or leflunomide may increase the risk of hepatotoxicity
3. **Heavy alcohol consumption** with oral muscle relaxants (e.g. baclofen)
Rationale: Concurrent alcohol consumption and muscle relaxants can increase the risk of CNS depression.

Malignant disease and immunosuppression

1. **Any alcohol consumption** with procarbazine
Rationale: A disulfram-like reaction can occur when alcohol is given with procarbazine
2. **Heavy alcohol consumption** with interferon alpha or interferon beta
Rationale: Heavy alcohol consumption combined with interferons may increase the risk of hepatotoxicity and reduce the response to treatment with interferon.

Infections

1. **Heavy alcohol consumption** with anti-mycobacterial medications such as isoniazid, pyrazinamide, ethionamide and rifampicin (alone or in combination)
Rationale: Alcohol combined with anti-mycobacterial medications increase the risk of hepatotoxicity
2. **Any alcohol consumption** with cycloserine
Rationale: Alcohol consumption may increase the risk of seizures in patients taking cycloserine.
3. **Any alcohol consumption** with metronidazole or tinidazole
Rationale: A disulfram-like reaction can occur when alcohol is given with metronidazole

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Consensus Validation of the POSAMINO (POtentially Serious Alcohol Medication INteractions in Older adults) Criteria

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Consensus Validation of the POSAMINO (POtentially Serious Alcohol Medication INteractions in Older adults) Criteria

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Abstract:

Objectives: Older adults are particularly vulnerable to adverse effects from concurrent alcohol and medication use. However, there is limited evidence regarding the prevalence of these adverse outcomes among older adults and there is a lack of consensus regarding what constitutes an alcohol-interactive medicine. The objective of this study was to develop an explicit list of potentially serious alcohol-medication interactions for use in older adults.

Design: Following a systematic review, review of drug compendia and clinical guidance documents, a two-round Delphi consensus method was conducted.

Setting: Ireland and the United Kingdom (UK), primary care and hospital setting.

Participants: The Project Steering Group developed a list of potentially serious alcohol-medication interactions. The Delphi panel consisted of 19 healthcare professionals (general practitioners (GPs), geriatricians, hospital and community pharmacists, clinical pharmacologists and pharmacists and physicians specialising in substance misuse).

Results: An inventory of 52 potentially serious alcohol-medication interactions was developed by the Project Steering Group. British National Formulary (BNF) black dot warnings (n=8) were included in the final criteria as they represent 'potentially serious' interactions. The remaining 44 criteria underwent a two-round Delphi process. In the first round, thirteen criteria were accepted into the POSAMINO criteria. Consensus was not reached on the remaining 31 criteria; nine were removed, and eight additional criteria were included following a review of panellist comments. The remaining 30 criteria went to round-two, with 17 criteria reaching consensus, providing a final list of 38 potentially serious alcohol-medication interactions; central nervous system (n=15), cardiovascular system (n=9), endocrine system (n=5), musculoskeletal system (n=3), infections (n=3), malignant disease & immunosuppression (n=2) and respiratory system (n=1).

Conclusions: POSAMINO is the first set of explicit potentially serious alcohol-medication interactions for use in older adults. These criteria will facilitate the risk stratification of older adults at the point of prescribing.

Strengths and limitations of this study:

- The potentially serious alcohol-medication interactions for use in older adults (POSAMINO) criteria were developed in a robust fashion, using a two-step process involving a systematic review and two-round Delphi process.
- The Delphi consensus technique utilised in this study is flexible and enabled communication from a diverse group of healthcare professionals from both the United Kingdom and Ireland.
- The final criteria will need to be further validated prospectively to quantify the magnitude of risk posed for each criterion for adverse outcomes in older adults.
- Once validated, these criteria have the potential to inform medical decision making and enable healthcare professionals to risk stratify older adults at the point of prescribing and prioritise alcohol screening and brief interventions in high-risk groups.

Background

Population demographics are changing globally, with the proportion and age of the older population continuing to increase. (1) While alcohol consumption tends to decline in older age, recent evidence suggests that drinking occasions tend to become more frequent among older adults. (2) There is also evidence of a cohort effect with successive birth cohorts reporting an increase in alcohol consumption among all age groups, including older adults. (3) Ageing is associated with a variety of physiological changes, which may place older adults at an increased risk of alcohol-related health problems. (4, 5) In fact, older adults experience a disproportionate burden of alcohol related-harm; in England between 2009 and 2010, adults aged ≥ 65 years accounted for approximately 44% (461,400) of alcohol-related hospital admissions yet comprised of only 17% of the population. (5) Alcohol-related deaths were also highest among those aged 55 to 74 years.(5)

Polypharmacy is also increasing in older adults. (6) For example, approximately 60% of Irish adults aged ≥ 65 years reported taking five or more medicines in 2012. (6) Certain medicines have the potential to interact with alcohol increasing the risk of medical complications such as hypoglycaemia, hypotension, sedation, gastrointestinal bleeds and liver damage. (7, 8) Alcohol interactive (AI) medicines may interact with alcohol by altering the metabolism (pharmacokinetic) or effects (pharmacodynamic) of alcohol and/or the medication. (8) Interactions may occur with any alcohol or follow a dose response, with the risk or severity of an interaction increasing with increasing levels of alcohol consumption. (7)

While a number of studies have investigated the concurrent use of alcohol and medicines with potential to interact with alcohol among older adults, (9-28) there is a lack of consensus regarding what constitutes an AI medication across studies. Several studies focussed on a wide range of medications, using different drug compendia to identify medications as alcohol interactive, thus leading to a lack of consistency in the inclusion of medicines as alcohol interactive. (9-12, 16, 19, 21-23) Other studies focussed on psychotropic medications alone. (13, 15, 17, 18, 20, 24, 26, 28)

While there appears to be a high propensity for alcohol-medication interactions among community dwelling older adults, with between one-in-five to one-in-three older adults potentially susceptible to alcohol-medication interactions, (11, 12, 23) no study to date has examined longitudinal associations of concurrent use

with adverse outcomes. An evidence based list of medications which have a significant risk of harm to older patients when combined with alcohol has potential in a clinical setting, once validated, allowing for the identification of older adults whose alcohol consumption places them at increased risk and who would benefit from a preventative intervention. Therefore, the aim of this study is to derive the first set of explicit potentially serious alcohol-medication interactions in older adults.

Methods

Study design

A Delphi consensus technique was used to develop the list of potentially serious alcohol-medication interactions in older adults. The Delphi method allows a consensus opinion to be reached amongst a panel of experts through an iterative process of questionnaires. (29) Ethics approval for this study was obtained from the Royal College of Surgeons in Ireland (Reference Number REC1097). A Project Steering Group comprising of academic and clinical pharmacists, a general practitioner and an epidemiologist (authors) from the RCSI School of Pharmacy and HRB Primary Care Centre was formed to develop the initial list of potentially serious alcohol-medication interactions and to later oversee the Delphi consensus study.

Compilation of initial list of potentially serious alcohol-medication interactions

Following a comprehensive systematic search using MEDLINE (PubMed), Embase, Scopus and Web of Science databases (30), an extensive list of medications with potential to interact with alcohol was identified by the Project Steering Group. A combination of the following keywords and MeSH terms were used: "ethanol", "alcohol", "drug interactions", "drug alcohol interaction" and "aged". This search was supplemented by a search in Google Scholar and by hand searching references of retrieved articles. The search was restricted to English language articles and articles published since January 1990. Furthermore, the British National Formulary (BNF), Stockley's Drug Interactions and Martindale Complete Drug Reference drug compendia were also searched. (31-33) Additional documents such as clinical guidance documents (34) and previous reviews (7, 8) were also accessed. Information extracted included: medication name/class, potential adverse outcome(s), whether an interaction is likely to occur with any alcohol consumption or with heavy consumption using national low risk drinking guidelines (35, 36) and, if reported, evidence supporting the interaction. The list of medications was organised according to the BNF physiological classification system. There was considerable heterogeneity across reference sources in terms of identifying medications as having potential to interact with alcohol, with no age specific information for interactions. Furthermore, there were inconsistencies in relation to the quantity of concurrent alcohol consumption that should be avoided. For

example, the Martindale mentioned that alcohol combined with NSAIDs may increase the risk of gastrointestinal bleeds with no mention of alcohol consumption patterns, Stockley's described that both NSAIDs and excessive alcohol use carry the risk of gastrointestinal adverse effects, while NSAIDs and alcohol were not included as an interaction in the BNF. For the next step, the Project Steering Group reviewed and assessed each medication or drug class. Using the definition of "necessary to avoid" previously described by Dreischulte et al. (37), it was considered necessary to avoid concurrent alcohol with a specific medication if, in an average older adult concurrent use of alcohol with this medication would be considered unsafe because (a) there is sufficient evidence that the patient is likely to be harmed, and (b) the likely harm to the patient is large enough to be clinically significant.

Drugs were excluded for the following reasons: their interaction with alcohol was not considered serious i.e. unlikely to cause significant harm to the patient (for example SSRIs and alcohol) (33); the medication is not licensed for use in older adults; the medication is only administered in a hospital environment (for example Trabectedin), interaction with alcohol may only occur during alcohol withdrawal or has been withdrawn from the market in the UK or Ireland. Following these exclusions a truncated list was further reviewed by the Project Steering Group by a consensus discussion. In this process the Project Steering Group agreed, that BNF black dot warnings would be included in the final list. BNF black dots refer to potentially serious drug-alcohol interactions where concurrent use should be avoided or only undertaken with caution and appropriate management. In the paper version of the BNF, these potentially serious drug-alcohol interactions are highlighted to prescribers by flagging them with a 'black dot' (31). Furthermore, the amount of alcohol to be avoided with each medication class was defined through group discussion, based on both the evidence available and the members' own clinical experience. Additionally, it was agreed that the following adverse outcomes associated with concurrent use were defined using clinical guidance documents and reviews to ensure clarity among all participants: orthostatic hypotension (38), hypoglycaemia (39) and lactic acidosis (40).

Selection of the Delphi panel

A total of 51 experts from the Republic of Ireland and United Kingdom, were invited (via e-mail or letter) to participate as part of the Delphi consensus panel. The experts invited to participate on the Delphi consensus panel were peer recognized by the Project Steering Group or nominated by other panel members on the basis of their clinical experience or knowledge of alcohol-medication interactions or care of older persons.

Reasons for non-participation were not required; however in some instances they were provided, they included time commitments and lack of clinical knowledge of alcohol-medication interactions. In total, 19 participants (37%) agreed to participate and written consent was received from all participants before the study. The panel consisted of general practitioners (GPs) (n=5), geriatricians (n=3), hospital pharmacists with expertise in care of older adults (n=3), community pharmacists (n=3), clinical pharmacologists (n=2), clinical pharmacists specialising in substance misuse (n=2) and a physician specialising in substance misuse (n=1). Panel members were not provided with compensation for participation.

The Delphi validation technique and process

An online questionnaire was piloted by two pharmacists and two GPs, to identify any potential problems and to approximate the completion time for the survey. Following amendments, the 19 participants were sent a link to the online POSAMINO questionnaire (via SurveyGizmo®) in March 2016. Participants were given four weeks to complete the online questionnaire and all participants were sent a reminder email after 2 weeks to encourage participation. The questionnaire was both anonymous and confidential.

The quantity of alcohol per standard drink (SD) (10 grammes alcohol in Ireland) or unit (8 grammes alcohol in the United Kingdom), was defined at the beginning of the survey. As some interactions are listed with any alcohol consumption and others with 'heavy' consumption, we provided definitions of both at the beginning of the questionnaire. Any alcohol consumption was defined as ≥1 SD of alcohol in Ireland or ≥1 unit of alcohol in the UK, with heavy consumption defined according to Irish and UK National low risk drinking guidelines. (35, 36) The panel were instructed to evaluate each potential interaction listed according to the "necessary to avoid" framework described above. (37) Medications were categorised according to the BNF

physiological classification system. Each statement was presented in the same format stating: It is necessary to avoid [quantity of alcohol] (any or heavy) with [medications/ drug class], followed by a brief rationale for the statement. For example: *It is necessary to avoid: Any alcohol consumption with first generation anti-histamines (for example promethazine). (Rationale: Concurrent alcohol consumption with first generation anti-histamines can increase the risk of sedation).*

Participants were asked to rate their agreement with each statement, using a 5-point Likert scale (1-strongly disagree to 5-strongly agree) along with any additional comments, or suggestions for additional medicines to be included.

After each round, the median and interquartile ranges (IQR) were calculated for each statement. Consistent with previous Delphi consensus studies, the consensus level required for a statement to be retained was defined *a priori* as a median of 4 or 5 with a lower quartile value of ≥ 4. (41) If a statement had an upper quartile value of ≤ 2, this indicated there was general disagreement with the statement between panel members, and the statement was rejected. If group consensus was not reached, the criteria were reviewed by the Project Steering Group and were removed based on comments or revised and included in the second questionnaire. In the second questionnaire, panellists were provided with links to the most recent evidence relating to each of the alcohol-medication interactions, to help facilitate their decisions due to uncertainty in round 1. As with round one, the median response and IQR were calculated and evaluated by the Project Steering Group using the same thresholds to determine consensus between the panel members. If consensus was not reached following the second round, the statement was rejected. Statistical analysis was performed using STATA version 13 and Microsoft Excel 2010.

Results

Following an initial review of the literature, Anatomical Therapeutic Chemical (ATC) codes for a total of 364 AI medicines were extracted by the Project Steering Group **(Supplementary File 1)**. Medicines were classified according to drug classes and organised according to BNF physiological classification systems. From this list, a total of 63 statements were initially compiled based on the 'necessary to avoid' framework. (37) Following group discussions, 11 statements were removed/updated or merged together, based on the steering groups clinical knowledge or experience with medicines. For example, the steering group decided to no longer classify benzodiazepines according to the duration of action, as both long acting and short acting have the potential to interact with alcohol. Furthermore, a total of eight BNF black dot warnings were included in the final criteria as they represent potentially serious interactions.

All 19 panel members completed the round one questionnaire, in which forty-four statements were presented. Consensus was reached on 13 statements, with no statements rejected **(Table 1)**. Thirty one statements were reviewed by the steering group, with nine statements removed based on comments from the panel, if the interaction was not relevant to older adults or the interaction was not of clinical significance for example: heavy alcohol consumption with vitamin A preparations. Furthermore, eight new statements were included in round two based on comments from panellists at the first round.

A total of 18 out of the 19 recruited participants completed the round two questionnaire. Of the 30 statements included in the second questionnaire, consensus was reached for 17 statements. The remaining 13 statements were rejected as no consensus was reached. In total, consensus was reached for 30 potentially serious drug alcohol interactions in older adults, with the inclusion of BNF black dot warnings the final list was 38 statements.

INSERT TABLE 1 HERE

This final 38 item POSAMINO criteria **(Table 2)** were organised over the following physiological systems: Central nervous system (n=15), cardiovascular system **(**n=9), endocrine system (n=5), musculoskeletal system (n=3), infections (n=3), malignant disease and immunosuppression (n=2) and respiratory system (n=1).

INSERT TABLE 2 HERE

Discussion

Principle findings in relation to previous studies

While older adults experience a disproportionate burden of alcohol related harm, (5) research suggests that healthcare professionals are less likely to discuss alcohol consumption with older adults. (42, 43) Flagging older adults at the point of prescribing an alcohol-interactive medication may facilitate targeted screening and interventions to help reduce harm. Despite the high propensity for alcohol-medication interactions among community dwelling older adults, our recent systematic review has highlighted that there is still a lack of consensus regarding what constitutes an AI medication.(30)

This study reports the development of a set of 38 explicit criteria, POSAMINO, for identifying older adults at risk of potentially serious alcohol-medication interactions. The final POSAMINO criteria consist of seven different drug classes, with central nervous system (CNS) medicines representing 40% of the criteria. Estimates from our previous study indicate that approximately one in five older Irish adults are exposed to CNS agents, with over half of patients using CNS agents also reporting concurrent alcohol consumption. (12) Nine of the final 38 criteria concern cardiovascular agents, another widely used drug class among aged adults. (12) There is also a high-risk of adverse effects associated with these agents, with anti-platelets, diuretics and anticoagulants identified as the most common drug classes involved in preventable drug-related admissions, in a previous study. (44) Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, paracetamol and gabapentin (used for neuropathic pain) were also included in the final POSAMINO criteria. (44) The prevalence of chronic pain increases with age and older adults may consume alcohol to help cope and manage their pain. (45) This behaviour may also predispose older adults to adverse outcomes associated with concurrent use with analgesics (for example increased sedation, falls and gastrointestinal bleeds).

The development of the POSAMINO criteria is important for several reasons. In the absence of an explicit list of alcohol-interactive medications, multiple drug reference sources have been used in previous studies leading to a lack of consistency in the inclusion of medications across studies, (11, 12, 19, 22, 23) which may result in biased estimates of potential risk among older adults. Furthermore, some of these interactions may be theoretical with trivial clinical significance. Therefore, this study developed a consensus-based set of explicit

criteria for potentially serious alcohol-medication interactions in older adults rather than an exhaustive list of medications with potential to interact with alcohol. Consistent with existing literature, the POSAMINO criteria classify CNS agents as AI medications with the potential to cause serious harm to older adults (9-13, 15-24, 26, 28). However, some of the previous studies focussed on sedatives/hypnotics only (13, 26, 28). We identified a number of additional CNS agents, such as anti-Parkinson's drugs (for example: Pramipexole, Apomorphine and Levodopa), which may be overlooked if we focus solely on sedatives or hypnotics.

Furthermore, the POSAMINO criteria also includes a wide range of other drug classes, such as cardiovascular, respiratory system, musculoskeletal, malignant disease, infections or endocrine agents which were not all considered among previous studies (9-11, 16, 19, 21, 23). It is also important to note that there has been little emphasis on the adverse outcomes or severity of these potential interactions.(22, 30) The development of the POSAMINO criteria may help identify older adults at risk of potentially serious alcohol-medicine interactions in the future.

Clinical implications and future research

This study adds to a growing body of research investigating the concurrent use of alcohol and alcohol interactive medicines in older adults. Undoubtedly, adverse drug events (ADEs) represent a major burden on healthcare, with ADEs detected in 26.3% of patients aged ≥ 65 years admitted to an Irish hospital with acute illnesses. (46) The increasing use of multiple medications, (6) combined with an increased frequency of alcohol consumption (2) and age-related physiological changes, may predispose older adults to these adverse events. The significant burden of alcohol-related harm and mortality among older adults, (5) indicates a pressing need for future interventions to minimise risk. However, prior to informing clinical or public health initiatives, the final criteria developed from this study, will require further validation to prospectively quantify the magnitude of risk posed for each criterion for adverse outcomes in older adults. In particular, the quantity of alcohol specified in each criterion will need to be further evaluated in prospective studies. Once validated, these criteria have the potential to inform medical decision making and enable healthcare professionals to risk stratify older adults at the point of prescribing and prioritise alcohol screening and brief interventions in high-

risk groups. This is essential, as older people have previously reported little knowledge about risks associated with the concurrent use of alcohol and medications. (47)

Strengths and Limitations

The criteria were developed in a robust fashion, using a two-step process involving a systematic review and two-round Delphi process. The Delphi technique is flexible and for this study enabled communication from a group of nineteen healthcare professionals from both the United Kingdom and Ireland. Eighteen of the 19 participants completed the two rounds, with participants providing numerous comments and suggestions in both rounds. Similar to previous studies, participants remained anonymous and were not provided with feedback following the first round in order to remove the risk of potential bias. (41)

Inevitably, there were limitations to this Delphi study. With all Delphi studies, participants' judgement may be subjective. In order to reduce this potential bias, a diverse group of healthcare professionals with expertise or interest in the care of older adults were selected. With explicit criteria, there is also a need for regular updates and revision due to the availability of more up to date information after development. (48) The developed POSAMINO criteria do not apply to older adults diagnosed with an alcohol use disorder, as chronic heavy alcohol consumption can substantially increase the activity of the cytochrome P450 metabolising enzyme CYP2E1. (8) Finally, older adults may also experience chronic illnesses which affect the metabolism of both alcohol and medications. As a result, it is important that healthcare professionals also consider these comorbid diseases when assessing the risk for potential adverse outcomes. (49)

Conclusions

Using a systematic review and a two-round Delphi consensus method, we have developed the first set of explicit potentially serious alcohol-medication interactions (POSAMINO) for use in older adults. Following future validation studies, these criteria may allow for the risk stratification of older adults at the point of prescribing, and prioritise alcohol screening and brief alcohol interventions in high-risk groups.

Declarations:

Authors' contributions: AH, PG, CR, TF & GC (the project steering group) conceived and designed this study. AH & GC conducted initial literature search. AH communicated with Delphi participants. AH analysed the data after each round. All Project Steering Group members were involved in interpretation of the data. AH & GC drafted the manuscript. All co-authors revised the manuscript and have given the approval for publication.

Competing interests: The authors declare that they have no competing interests.

Ethics approval: Ethical approval for this study was approved by the Royal College of Surgeons in Ireland (RCSI) ethics committee (REC 1097).

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Data sharing statement: Additional data is available by request from the corresponding author.

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Table 1: Results from the 2-round Delphi process

	Potentially serious interactions as listed in the BNF	Round 1					Round 2					Final Criteria
Physiological System		**Total**	**Accept**	**Revise**	**Reject**	**Removal**	**New statements included**	**Total**	**Accept**	**Revise**	**Reject**	
Cardiovascular System	1	14	1	13	0	3	2	12	7	0	5	9
Respiratory System	0	1	1	0	0	0	0	0	0	0	0	1
Central Nervous System	4	12	6	6	0	1	5	10	5	0	5	15
Infections	2	5	0	5	0	3	0	2	1	0	1	3
Endocrine System	0	5	3	2	0	0	0	2	2	0	0	5
Obstetrics, Gynaecology, and Urinary Tract Disorders	0	2	0	2	0	1	1	2	0	0	2	0
Malignant Disease and Immunosuppression	1	1	0	1	0	0	0	1	1	0	0	2
Nutrition and Blood	0	1	0	1	0	1	0	0	0	0	0	0
Musculoskeletal System	0	3	2	1	0	0	0	1	1	0	0	3
Total	**8**	**44**	**13**	**31**	**0**	**9**	**8**	**30**	**17**	**0**	**13**	**38**

Table 2: Final POSAMINO Criteria (n=38)

Cardiovascular System

1. **Heavy alcohol consumption** with multiple anti-hypertensive combinations
   Rationale: Concurrent use of alcohol consumption and anti-hypertensives may increase the risk of orthostatic hypotension
2. **Heavy alcohol consumption** with warfarin (& phenindione)
   Rationale: Heavy episodic alcohol consumption is associated with an increased risk of major bleeds
3. **Heavy alcohol consumption** with regular use of low dose aspirin (75mg)
   Rationale: Heavy alcohol consumption combined with aspirin may cause a small increase in gastrointestinal blood loss
4. **Heavy alcohol consumption** with both regular and as required nitrates (e.g. glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate)
   Rationale: The combined haemodynamic effects of alcohol and nitrates, increases the risk of exaggerated hypotension.
5. **Heavy alcohol consumption** with the vasodilatory medication nicorandil
   Rationale: The combined haemodynamic effects of alcohol & nicorandil; increases the risk of exaggerated hypotension.
6. **Heavy alcohol consumption** with the combined use of both nitrates and vasodilator medication (e.g. nicorandil)
   Rationale: The combined haemodynamic effects of alcohol and nitrates, increases the risk of exaggerated hypotension.
7. **Heavy alcohol consumption** with diuretics (e.g. loop diuretics (furosemide), thiazide diuretics (bendroflumethiazide) & potassium sparing diuretics (amiloride))
   Rationale: The concurrent use of alcohol and anti-hypertensives may increase the risk of orthostatic hypotension.
8. **Heavy alcohol consumption** with alpha blockers (e.g. terazosin)
   Rationale: The concurrent use of alcohol and anti-hypertensives may increase the risk of orthostatic hypotension.
9. **Heavy alcohol consumption** with centrally acting anti-hypertensives (e.g. clonidine or methyldopa)
   Rationale: Alcohol consumption combined with centrally acting anti-hypertensives may increase the risk of sedation.

Respiratory System

1. **Any alcohol consumption** with first generation anti-histamines (e.g. promethazine)
   Rationale: Concurrent alcohol consumption with first generation anti-histamines can increase the risk of sedation

Central Nervous System

1. **Heavy alcohol consumption** with benzodiazepines (e.g.diazepam) and benzodiazepine related medications (e.g.zopiclone)
   Rationale: Alcohol consumption combined with benzodiazepines and benzodiazepine related medications may enhance CNS depressant effects
2. **Heavy alcohol consumption** combined with opioids
   Rationale: Alcohol consumption combined with opioids may enhance CNS depressant effects of alcohol
3. **Heavy alcohol consumption** with duloxetine
   Rationale: Heavy alcohol consumption combined with duloxetine may increase the risk of hepatotoxicity
4. **Heavy alcohol consumption** with all anti-psychotics
   Rationale: Alcohol consumption combined with antipsychotics may increase the risk of sedation
5. **Any alcohol consumption** with barbiturates
   Rationale: Alcohol consumption combined with barbiturates may increase the risk of sedation.
6. **Heavy alcohol consumption** with anti-epileptic drugs (AEDs)
   Rationale: Heavy alcohol consumption can increase the risk of seizures and sedation in patients taking AEDs.
7. **Any alcohol consumption** with tricyclic anti-depressants (TCAs)
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
8. **Any alcohol consumption** with tetracyclic antidepressants
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
9. **Any alcohol consumption** with mirtazapine
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
10. **Any alcohol consumption** with monoamine oxidase inhibitors (MAOIs)
    Rationale: A potentially life-threatening hypertensive reaction can develop in patients taking non-selective MAOIs who consume drinks rich in tyramine (e.g. wines, beers and non-alcoholic beers)
11. **Heavy alcohol consumption** with long term regular paracetamol use (e.g. 1g four times a day)
    Rationale: Heavy alcohol consumption may increase the risk of paracetamol hepatotoxicity especially if alcohol intake is abruptly stopped.
12. **Heavy alcohol consumption** with gabapentin (when used for neuropathic pain)
    Rationale: Alcohol combined with medications for neuropathic pain may increase the risk of sedation
13. **Heavy alcohol consumption** with pramipexole or amantadine
    Rationale: Alcohol may increase the risk of sedation
14. **Heavy alcohol consumption** with apomorphine
    Rationale: Alcohol combined with apomorphine may increase the risk of orthostatic hypotension

15. **Heavy alcohol consumption** with levodopa (alone or in combination with carbidopa)
Rationale: Alcohol combined with levodopa (alone or in combination with carbidopa) may increase the risk of orthostatic hypotension.

Endocrine

1. **Heavy alcohol consumption** with insulin
Rationale: Alcohol consumption may enhance the hypoglycaemic effect of insulin.
2. **Heavy alcohol consumption** with metformin
Rationale: Heavy alcohol consumption combined with metformin may increase the risk of lactic acidosis
3. **Heavy alcohol consumption** with sulphonylureas
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics
4. **Heavy alcohol consumption** with meglitinides (e.g. nateglinide)
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics
5. **Heavy alcohol consumption** with thiazolidinediones (e.g. pioglitazone)
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics

Musculoskeletal and joint diseases

1. **Heavy alcohol consumption** with any nonsteroidal anti-inflammatory drugs NSAIDs (including COX-2 inhibitors)
Rationale: Heavy alcohol consumption and NSAID use carry an increased risk of gastrointestinal bleeds
2. **Heavy alcohol consumption** combined with methotrexate or leflunomide
Rationale: Heavy alcohol consumption combined with methotrexate or leflunomide may increase the risk of hepatotoxicity
3. **Heavy alcohol consumption** with oral muscle relaxants (e.g. baclofen)
Rationale: Concurrent alcohol consumption and muscle relaxants can increase the risk of CNS depression.

Malignant disease and immunosuppression

1. **Any alcohol consumption** with procarbazine
Rationale: A disulfram-like reaction can occur when alcohol is given with procarbazine
2. **Heavy alcohol consumption** with interferon alpha or interferon beta
Rationale: Heavy alcohol consumption combined with interferons may increase the risk of hepatotoxicity and reduce the response to treatment with interferon.

Infections

1. **Heavy alcohol consumption** with anti-mycobacterial medications such as isoniazid, pyrazinamide, ethionamide and rifampicin (alone or in combination)
Rationale: Alcohol combined with anti-mycobacterial medications increase the risk of hepatotoxicity
2. **Any alcohol consumption** with cycloserine
Rationale: Alcohol consumption may increase the risk of seizures in patients taking cycloserine.
3. **Any alcohol consumption** with metronidazole or tinidazole
Rationale: A disulfram-like reaction can occur when alcohol is given with metronidazole

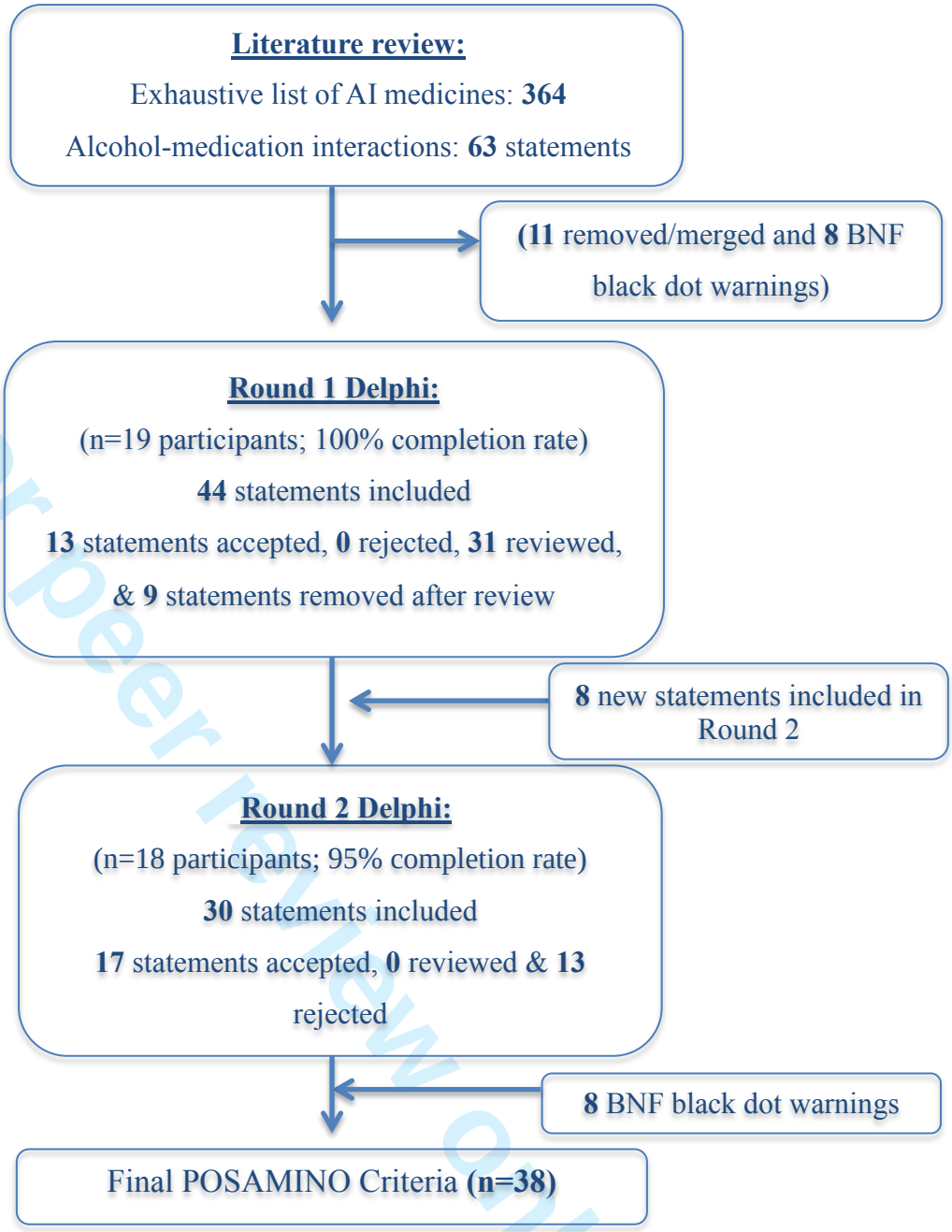

Figure 1: Flow chart summarizing the steps involved in the development of the POSAMINO criteria

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Consensus Validation of the POSAMINO (POtentially Serious Alcohol Medication INteractions in Older adults) Criteria

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Consensus Validation of the POSAMINO (POtentially Serious Alcohol Medication INteractions in Older adults) Criteria

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Abstract:

Objectives: Older adults are particularly vulnerable to adverse effects from concurrent alcohol and medication use. However, there is limited evidence regarding the prevalence of these adverse outcomes among older adults and there is a lack of consensus regarding what constitutes an alcohol-interactive medicine. The objective of this study was to develop an explicit list of potentially serious alcohol-medication interactions for use in older adults.

Design: Following a systematic review, review of drug compendia and clinical guidance documents, a two-round Delphi consensus method was conducted.

Setting: Ireland and the United Kingdom (UK), primary care and hospital setting.

Participants: The Project Steering Group developed a list of potentially serious alcohol-medication interactions. The Delphi panel consisted of 19 healthcare professionals (general practitioners (GPs), geriatricians, hospital and community pharmacists, clinical pharmacologists and pharmacists and physicians specialising in substance misuse).

Results: An inventory of 52 potentially serious alcohol-medication interactions was developed by the Project Steering Group. British National Formulary (BNF) black dot warnings (n=8) were included in the final criteria as they represent 'potentially serious' interactions. The remaining 44 criteria underwent a two-round Delphi process. In the first round, thirteen criteria were accepted into the POSAMINO criteria. Consensus was not reached on the remaining 31 criteria; nine were removed, and eight additional criteria were included following a review of panellist comments. The remaining 30 criteria went to round-two, with 17 criteria reaching consensus, providing a final list of 38 potentially serious alcohol-medication interactions; central nervous system (n=15), cardiovascular system (n=9), endocrine system (n=5), musculoskeletal system (n=3), infections (n=3), malignant disease & immunosuppression (n=2) and respiratory system (n=1).

Conclusions: POSAMINO is the first set of explicit potentially serious alcohol-medication interactions for use in older adults. Following future validation studies, these criteria may allow for the risk stratification of older adults at the point of prescribing.

Strengths and limitations of this study:

- The potentially serious alcohol-medication interactions for use in older adults (POSAMINO) criteria were developed in a robust fashion, using a two-step process involving a systematic review and two-round Delphi process.
- The Delphi consensus technique utilised in this study is flexible and enabled communication from a diverse group of healthcare professionals from both the United Kingdom and Ireland.
- The final criteria will need to be further validated prospectively to quantify the magnitude of risk posed for each criterion for adverse outcomes in older adults.
- Once validated, these criteria have the potential to inform medical decision making and enable healthcare professionals to risk stratify older adults at the point of prescribing and prioritise alcohol screening and brief interventions in high-risk groups.

Background

Population demographics are changing globally, with the proportion and age of the older population continuing to increase. (1) While alcohol consumption tends to decline in older age, recent evidence suggests that drinking occasions tend to become more frequent among older adults. (2) There is also evidence of a cohort effect with successive birth cohorts reporting an increase in alcohol consumption among all age groups, including older adults. (3) Ageing is associated with a variety of physiological changes, which may place older adults at an increased risk of alcohol-related health problems. (4, 5) In fact, older adults experience a disproportionate burden of alcohol related-harm; in England between 2009 and 2010, adults aged ≥ 65 years accounted for approximately 44% (461,400) of alcohol-related hospital admissions yet comprised of only 17% of the population. (5) Alcohol-related deaths were also highest among those aged 55 to 74 years.(5)

Polypharmacy is also increasing in older adults. (6) For example, approximately 60% of Irish adults aged ≥ 65 years reported taking five or more medicines in 2012. (6) Certain medicines have the potential to interact with alcohol increasing the risk of medical complications such as hypoglycaemia, hypotension, sedation, gastrointestinal bleeds and liver damage. (7, 8) In one cross sectional study, after adjusting for potential confounders, moderate alcohol consumption was associated with a 24% increased risk in adverse drug reactions (ADRs) among older adults. (21) Alcohol interactive (AI) medicines may interact with alcohol by altering the metabolism (pharmacokinetic) or effects (pharmacodynamic) of alcohol and/or the medication. (8) Interactions may occur with any alcohol or follow a dose response, with the risk or severity of an interaction increasing with increasing levels of alcohol consumption. (7)

While a number of studies have investigated the concurrent use of alcohol and medicines with potential to interact with alcohol among older adults, (9-28) there is a lack of consensus regarding what constitutes an AI medication across studies. Several studies focussed on a wide range of medications, using different drug compendia to identify medications as alcohol interactive, thus leading to a lack of consistency in the inclusion of medicines as alcohol interactive. (9-12, 16, 19, 21-23) Other studies focussed on psychotropic medications alone. (13, 15, 17, 18, 20, 24, 26, 28)

While there appears to be a high propensity for alcohol-medication interactions among community dwelling older adults, with between one-in-five to one-in-three older adults potentially susceptible to alcohol-medication interactions, (11, 12, 23) no study to date has examined longitudinal associations of concurrent use with adverse outcomes. An evidence based list of medications which have a significant risk of harm to older patients when combined with alcohol has potential in a clinical setting, once validated, allowing for the identification of older adults whose alcohol consumption places them at increased risk and who would benefit from a preventative intervention. Therefore, the aim of this study is to derive the first set of explicit potentially serious alcohol-medication interactions in older adults.

Methods

Study design

A Delphi consensus technique was used to develop the list of potentially serious alcohol-medication interactions in older adults. The Delphi method allows a consensus opinion to be reached amongst a panel of experts through an iterative process of questionnaires. (29) Ethics approval for this study was obtained from the Royal College of Surgeons in Ireland (RCSI) (Reference Number REC1097). A Project Steering Group comprising of academic and clinical pharmacists, a general practitioner and an epidemiologist (authors) from the RCSI School of Pharmacy and Health Research Board (HRB) Primary Care Centre was formed to develop the initial list of potentially serious alcohol-medication interactions and to later oversee the Delphi consensus study.

Compilation of initial list of potentially serious alcohol-medication interactions

Following a comprehensive systematic search using MEDLINE (PubMed), Embase, Scopus and Web of Science databases (30), an extensive list of medications with potential to interact with alcohol was identified by the Project Steering Group. A combination of the following keywords and MeSH terms were used: "ethanol", "alcohol", "drug interactions", "drug alcohol interaction" and "aged". This search was supplemented by a search in Google Scholar and by hand searching references of retrieved articles. The search was restricted to English language articles and articles published since January 1990. Furthermore, the British National Formulary (BNF), Stockley's Drug Interactions and Martindale Complete Drug Reference drug compendia were also searched. (31-33) Additional documents such as clinical guidance documents (34) and previous reviews (7, 8) were also accessed. Information extracted included: medication name/class, potential adverse outcome(s), whether an interaction is likely to occur with any alcohol consumption or with heavy consumption using national low risk drinking guidelines (35, 36) and, if reported, evidence supporting the interaction. The list of medications was organised according to the BNF physiological classification system. There was considerable heterogeneity across reference sources in terms of identifying medications as having potential to interact with alcohol, with no age specific information for interactions. Furthermore, there were

inconsistencies in relation to the quantity of concurrent alcohol consumption that should be avoided. For example, the Martindale mentioned that alcohol combined with nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of gastrointestinal bleeds with no mention of alcohol consumption patterns, Stockley's described that both NSAIDs and excessive alcohol use carry the risk of gastrointestinal adverse effects, while NSAIDs and alcohol were not included as an interaction in the BNF. For the next step, the Project Steering Group reviewed and assessed each medication or drug class. Using the definition of "necessary to avoid" previously described by Dreischulte et al. (37), it was considered necessary to avoid concurrent alcohol with a specific medication if, in an average older adult concurrent use of alcohol with this medication would be considered unsafe because (a) there is sufficient evidence that the patient is likely to be harmed, and (b) the likely harm to the patient is large enough to be clinically significant.

Drugs were excluded for the following reasons: their interaction with alcohol was not considered serious i.e. unlikely to cause significant harm to the patient (for example: selective serotonin reuptake inhibitors (SSRIs) and alcohol) (33); the medication is not licensed for use in older adults; the medication is only administered in a hospital environment (for example Trabectedin), interaction with alcohol may only occur during alcohol withdrawal or has been withdrawn from the market in the UK or Ireland. Following these exclusions a truncated list was further reviewed by the Project Steering Group by a consensus discussion. In this process the Project Steering Group agreed, that BNF black dot warnings would be included in the final list. BNF black dots refer to potentially serious drug-alcohol interactions where concurrent use should be avoided or only undertaken with caution and appropriate management. In the paper version of the BNF, these potentially serious drug-alcohol interactions are highlighted to prescribers by flagging them with a 'black dot' (31). Furthermore, the amount of alcohol to be avoided with each medication class was defined through group discussion, based on both the evidence available and the members' own clinical experience. Additionally, it was agreed that the following adverse outcomes associated with concurrent use were defined using clinical guidance documents and reviews to ensure clarity among all participants: orthostatic hypotension (38), hypoglycaemia (39) and lactic acidosis (40).

Selection of the Delphi panel

A total of 51 experts from the Republic of Ireland and United Kingdom (UK), were invited (via e-mail or letter) to participate as part of the Delphi consensus panel. The experts invited to participate on the Delphi consensus panel were peer recognized by the Project Steering Group or nominated by other panel members on the basis of their clinical experience or knowledge of alcohol-medication interactions or care of older persons.

Reasons for non-participation were not required; however, in some instances they were provided, they included time commitments and lack of clinical knowledge of alcohol-medication interactions. In total, 19 participants (37%) agreed to participate and written consent was received from all participants before the study. The panel consisted of general practitioners (GPs) (n=5), geriatricians (n=3), hospital pharmacists with expertise in care of older adults (n=3), community pharmacists (n=3), clinical pharmacologists (n=2), clinical pharmacists specialising in substance misuse (n=2) and a physician specialising in substance misuse (n=1). Panel members were not provided with compensation for participation.

The Delphi validation technique and process

An online questionnaire was piloted by two pharmacists and two GPs, to identify any potential problems and to approximate the completion time for the survey. Following amendments, the 19 participants were sent a link to the online POSAMINO questionnaire (via SurveyGizmo®) in March 2016. Participants were given four weeks to complete the online questionnaire and all participants were sent a reminder email after 2 weeks to encourage participation. The questionnaire was both anonymous and confidential.

The quantity of alcohol per standard drink (SD) (10 grammes alcohol in Ireland) or unit (8 grammes alcohol in the United Kingdom), was defined at the beginning of the survey. As some interactions are listed with any alcohol consumption and others with 'heavy' consumption, we provided definitions of both at the beginning of the questionnaire. Any alcohol consumption was defined as ≥1 SD of alcohol in Ireland or ≥1 unit of alcohol in the UK, with heavy consumption defined according to Irish and UK National low risk drinking guidelines. (35, 36) The panel were instructed to evaluate each potential interaction listed according to the

"necessary to avoid" framework described above. (37) Medications were categorised according to the BNF physiological classification system. Each statement was presented in the same format stating: It is necessary to avoid [quantity of alcohol] (any or heavy) with [medications/ drug class], followed by a brief rationale for the statement. For example: *It is necessary to avoid: Any alcohol consumption with first generation anti-histamines (for example promethazine). (Rationale: Concurrent alcohol consumption with first generation anti-histamines can increase the risk of sedation).*

Participants were asked to rate their agreement with each statement, using a 5-point Likert scale (1-strongly disagree to 5-strongly agree) along with any additional comments, or suggestions for additional medicines to be included.

After each round, the median and interquartile ranges (IQR) were calculated for each statement. Consistent with previous Delphi consensus studies, the consensus level required for a statement to be retained was defined *a priori* as a median of 4 or 5 with a lower quartile value of ≥ 4. (41) If a statement had an upper quartile value of ≤ 2, this indicated there was general disagreement with the statement between panel members, and the statement was rejected. If group consensus was not reached, the criteria were reviewed by the Project Steering Group and were removed based on comments or revised and included in the second questionnaire. In the second questionnaire, panellists were provided with links to the most recent evidence relating to each of the alcohol-medication interactions, to help facilitate their decisions due to uncertainty in round 1. As with round one, the median response and IQR were calculated and evaluated by the Project Steering Group using the same thresholds to determine consensus between the panel members. If consensus was not reached following the second round, the statement was rejected. Statistical analysis was performed using STATA version 13 and Microsoft Excel 2010.

Results

Following an initial review of the literature, Anatomical Therapeutic Chemical (ATC) codes for a total of 364 AI medicines were extracted by the Project Steering Group **(Supplementary File 1).** Medicines were classified according to drug classes and organised according to BNF physiological classification systems. From this list, a total of 63 statements were initially compiled based on the 'necessary to avoid' framework. (37) Following group discussions, 11 statements were removed/updated or merged together, based on the steering groups clinical knowledge or experience with medicines. For example, the steering group decided to no longer classify benzodiazepines according to the duration of action, as both long acting and short acting have the potential to interact with alcohol. Furthermore, a total of eight BNF black dot warnings were included in the final criteria as they represent potentially serious interactions.

All 19 panel members completed the round one questionnaire, in which forty-four statements were presented. Consensus was reached on 13 statements, with no statements rejected **(Table 1)**. Thirty-one statements were reviewed by the steering group, with nine statements removed based on comments from the panel, if the interaction was not relevant to older adults or the interaction was not of clinical significance for example: heavy alcohol consumption with vitamin A preparations. Furthermore, eight new statements were included in round two based on comments from panellists at the first round.

A total of 18 out of the 19 recruited participants completed the round two questionnaire. Of the 30 statements included in the second questionnaire, consensus was reached for 17 statements. The remaining 13 statements were rejected as no consensus was reached. In total, consensus was reached for 30 potentially serious drug alcohol interactions in older adults, with the inclusion of BNF black dot warnings the final list was 38 statements.

INSERT TABLE 1 HERE

This final 38 item POSAMINO criteria **(Table 2)** were organised over the following physiological systems: Central nervous system (n=15), cardiovascular system **(**n=9), endocrine system (n=5), musculoskeletal system (n=3), infections (n=3), malignant disease and immunosuppression (n=2) and respiratory system (n=1).

INSERT TABLE 2 HERE

Discussion

Principle findings in relation to previous studies

While older adults experience a disproportionate burden of alcohol related harm, (5) research suggests that healthcare professionals are less likely to discuss alcohol consumption with older adults. (42, 43) Flagging older adults at the point of prescribing an alcohol-interactive medication may facilitate targeted screening and interventions to help reduce harm. Despite the high propensity for alcohol-medication interactions among community dwelling older adults, our recent systematic review has highlighted that there is still a lack of consensus regarding what constitutes an AI medication. (30) This study reports the development of a set of 38 explicit criteria, POSAMINO, for identifying older adults at risk of potentially serious alcohol-medication interactions.

The final POSAMINO criteria consist of seven different drug classes, with central nervous system (CNS) medicines representing 40% of the criteria. Estimates from our previous study indicate that approximately one in five older Irish adults are exposed to CNS agents, with over half of patients using CNS agents also reporting concurrent alcohol consumption. (12) Nine of the final 38 criteria concern cardiovascular agents, another widely used drug class among aged adults. (12) There is also a high-risk of adverse effects associated with these agents, with anti-platelets, diuretics and anticoagulants identified as the most common drug classes involved in preventable drug-related admissions, in a previous study. (44) Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, paracetamol and gabapentin (used for neuropathic pain) were also included in the final POSAMINO criteria. The prevalence of chronic pain increases with age and older adults may consume alcohol to help cope and manage their pain. (45) This behaviour may also predispose older adults to adverse outcomes associated with concurrent use with analgesics (for example increased sedation, falls and gastrointestinal bleeds).

The development of the POSAMINO criteria is important for several reasons. In the absence of an explicit list of alcohol-interactive medications, multiple drug reference sources have been used in previous studies leading to a lack of consistency in the inclusion of medications across studies, (11, 12, 19, 22, 23) which may result in biased estimates of potential risk among older adults. Furthermore, some of these interactions may be

theoretical with trivial clinical significance. Therefore, this study developed a consensus-based set of explicit criteria for potentially serious alcohol-medication interactions in older adults rather than an exhaustive list of medications with potential to interact with alcohol. Consistent with existing literature, the POSAMINO criteria classify CNS agents as AI medications with the potential to cause serious harm to older adults. (9-13, 15-24, 26, 28) However, some of the previous studies focussed on sedatives/hypnotics only. (13, 26, 28) We identified a number of additional CNS agents, such as anti-Parkinson's drugs (for example: Pramipexole, Apomorphine and Levodopa), which may be overlooked if we focus solely on sedatives or hypnotics.

Furthermore, the POSAMINO criteria also includes a wide range of other drug classes, such as cardiovascular, respiratory system, musculoskeletal, malignant disease, infections or endocrine agents which were not all considered among previous studies. (9-11, 16, 19, 21, 23) It is also important to note that there has been little emphasis on the adverse outcomes or severity of these potential interactions. (22, 30) The development of the POSAMINO criteria may help identify older adults at risk of potentially serious alcohol-medicine interactions in the future.

Clinical implications and future research

This study adds to a growing body of research investigating the concurrent use of alcohol and alcohol interactive medicines in older adults. Undoubtedly, adverse drug events (ADEs) represent a major burden on healthcare, with ADEs detected in 26.3% of patients aged ≥ 65 years admitted to an Irish hospital with acute illnesses. (46) The increasing use of multiple medications, (6) combined with an increased frequency of alcohol consumption (2) and age-related physiological changes, may predispose older adults to these adverse events. The significant burden of alcohol-related harm and mortality among older adults, (5) indicates a pressing need for future interventions to minimise risk. However, prior to informing clinical or public health initiatives, the final criteria developed from this study, will require further validation to prospectively quantify the magnitude of risk posed for each criterion for adverse outcomes in older adults. In particular, the quantity of alcohol specified in each criterion will need to be further evaluated in prospective studies. Once validated, these criteria have the potential to inform medical decision making and enable healthcare professionals to risk stratify older adults at the point of prescribing and prioritise alcohol screening and brief interventions in high-

risk groups. This is essential, as older people have previously reported little knowledge about risks associated with the concurrent use of alcohol and medications. (47)

Strengths and Limitations

The criteria were developed in a robust fashion, using a two-step process involving a systematic review and two-round Delphi process. The Delphi technique is flexible and for this study enabled communication from a group of nineteen healthcare professionals from both the United Kingdom and Ireland. Eighteen of the 19 participants completed the two rounds, with participants providing numerous comments and suggestions in both rounds. Similar to previous studies, participants remained anonymous and were not provided with feedback following the first round in order to remove the risk of potential bias. (41)

Inevitably, there were limitations to this Delphi study. With all Delphi studies, participants' judgement may be subjective. In order to reduce this potential bias, a diverse group of healthcare professionals with expertise or interest in the care of older adults were selected. With explicit criteria, there is also a need for regular updates and revision due to the availability of more up to date information after development. (48) The developed POSAMINO criteria do not apply to older adults diagnosed with an alcohol use disorder, as chronic heavy alcohol consumption can substantially increase the activity of the cytochrome P450 metabolising enzyme CYP2E1. (8) Finally, older adults may also experience chronic illnesses which affect the metabolism of both alcohol and medications. As a result, it is important that healthcare professionals also consider these comorbid diseases when assessing the risk for potential adverse outcomes. (49)

Conclusions

Using a systematic review and a two-round Delphi consensus method, we have developed the first set of explicit potentially serious alcohol-medication interactions (POSAMINO) for use in older adults. Following future validation studies, these criteria may allow for the risk stratification of older adults at the point of prescribing, and prioritise alcohol screening and brief alcohol interventions in high-risk groups.

Declarations:

Authors' contributions: AH, PG, CR, TF & GC (the project steering group) conceived and designed this study. AH & GC conducted initial literature search. AH communicated with Delphi participants. AH analysed the data after each round. All Project Steering Group members were involved in interpretation of the data. AH & GC drafted the manuscript. All co-authors revised the manuscript and have given the approval for publication.

Competing interests: The authors declare that they have no competing interests.

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Table 1: Results from the 2-round Delphi process

	Potentially serious interactions as listed in the BNF	Round 1					Round 2					Final Criteria
Physiological System		**Total**	**Accept**	**Revise**	**Reject**	**Removal**	**New statements included**	**Total**	**Accept**	**Revise**	**Reject**	
Cardiovascular System	1	14	1	13	0	3	2	12	7	0	5	9
Respiratory System	0	1	1	0	0	0	0	0	0	0	0	1
Central Nervous System	4	12	6	6	0	1	5	10	5	0	5	15
Infections	2	5	0	5	0	3	0	2	1	0	1	3
Endocrine System	0	5	3	2	0	0	0	2	2	0	0	5
Obstetrics, Gynaecology, and Urinary Tract Disorders	0	2	0	2	0	1	1	2	0	0	2	0
Malignant Disease and Immunosuppression	1	1	0	1	0	0	0	1	1	0	0	2
Nutrition and Blood	0	1	0	1	0	1	0	0	0	0	0	0
Musculoskeletal System	0	3	2	1	0	0	0	1	1	0	0	3
Total	**8**	**44**	**13**	**31**	**0**	**9**	**8**	**30**	**17**	**0**	**13**	**38**

Table 2: Final POSAMINO Criteria (n=38)

Cardiovascular System

1. **Heavy alcohol consumption** with multiple anti-hypertensive combinations
   Rationale: Concurrent use of alcohol consumption and anti-hypertensives may increase the risk of orthostatic hypotension
2. **Heavy alcohol consumption** with warfarin (& phenindione)
   Rationale: Heavy episodic alcohol consumption is associated with an increased risk of major bleeds
3. **Heavy alcohol consumption** with regular use of low dose aspirin (75mg)
   Rationale: Heavy alcohol consumption combined with aspirin may cause a small increase in gastrointestinal blood loss
4. **Heavy alcohol consumption** with both regular and as required nitrates (e.g. glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate)
   Rationale: The combined haemodynamic effects of alcohol and nitrates may increase the risk of exaggerated hypotension.
5. **Heavy alcohol consumption** with the vasodilatory medication nicorandil
   Rationale: The combined haemodynamic effects of alcohol & nicorandil may increase the risk of exaggerated hypotension.
6. **Heavy alcohol consumption** with the combined use of both nitrates and vasodilator medication (e.g. nicorandil)
   Rationale: The combined haemodynamic effects of alcohol with nitrates and vasodilator drugs, may increase the risk of exaggerated hypotension.
7. **Heavy alcohol consumption** with diuretics (e.g. loop diuretics (furosemide), thiazide diuretics (bendroflumethiazide) & potassium sparing diuretics (amiloride))
   Rationale: The concurrent use of alcohol and anti-hypertensives may increase the risk of orthostatic hypotension.
8. **Heavy alcohol consumption** with alpha blockers (e.g. terazosin)
   Rationale: The concurrent use of alcohol and anti-hypertensives may increase the risk of orthostatic hypotension.
9. **Heavy alcohol consumption** with centrally acting anti-hypertensives (e.g. clonidine or methyldopa)
   Rationale: Alcohol consumption combined with centrally acting anti-hypertensives may increase the risk of sedation and/or orthostatic hypotension

Respiratory System

1. **Any alcohol consumption** with first generation anti-histamines (e.g. promethazine)
   Rationale: Concurrent alcohol consumption with first generation anti-histamines can increase the risk of sedation

Central Nervous System (CNS)

1. **Heavy alcohol consumption** with benzodiazepines (e.g.diazepam) and benzodiazepine related medications (e.g.zopiclone)
   Rationale: Alcohol consumption combined with benzodiazepines and benzodiazepine related medications may enhance CNS depressant effects
2. **Heavy alcohol consumption** combined with opioids
   Rationale: Alcohol consumption combined with opioids may enhance CNS depressant effects of alcohol
3. **Heavy alcohol consumption** with duloxetine
   Rationale: Heavy alcohol consumption combined with duloxetine may increase the risk of hepatotoxicity
4. **Heavy alcohol consumption** with all anti-psychotics
   Rationale: Alcohol consumption combined with antipsychotics may increase the risk of sedation
5. **Any alcohol consumption** with barbiturates
   Rationale: Alcohol consumption combined with barbiturates may increase the risk of sedation.
6. **Heavy alcohol consumption** with anti-epileptic drugs (AEDs)
   Rationale: Heavy alcohol consumption can increase the risk of seizures and sedation in patients taking AEDs.
7. **Any alcohol consumption** with tricyclic anti-depressants (TCAs)
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
8. **Any alcohol consumption** with tetracyclic antidepressants
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
9. **Any alcohol consumption** with mirtazapine
   Rationale: Alcohol consumption combined with antidepressants may enhance the CNS depressant effects of alcohol
10. **Any alcohol consumption** with monoamine oxidase inhibitors (MAOIs)
    Rationale: A potentially life-threatening hypertensive reaction can develop in patients taking non-selective MAOIs who consume drinks rich in tyramine (e.g. wines, beers and non-alcoholic beers)
11. **Heavy alcohol consumption** with long term regular paracetamol use (e.g. 1g four times a day)
    Rationale: Heavy alcohol consumption may increase the risk of paracetamol hepatotoxicity especially if alcohol intake is abruptly stopped.
12. **Heavy alcohol consumption** with gabapentin (when used for neuropathic pain)
    Rationale: Alcohol combined with medications for neuropathic pain may increase the risk of sedation
13. **Heavy alcohol consumption** with pramipexole or amantadine
    Rationale: Alcohol combined with pramipexole or amantadine may increase the risk of sedation
14. **Heavy alcohol consumption** with apomorphine
    Rationale: Alcohol combined with apomorphine may increase the risk of orthostatic hypotension

15. **Heavy alcohol consumption** with levodopa (alone or in combination with carbidopa)
Rationale: Alcohol combined with levodopa (alone or in combination with carbidopa) may increase the risk of orthostatic hypotension

Endocrine

1. **Heavy alcohol consumption** with insulin
Rationale: Alcohol consumption may enhance the hypoglycaemic effect of insulin
2. **Heavy alcohol consumption** with metformin
Rationale: Heavy alcohol consumption combined with metformin may increase the risk of lactic acidosis
3. **Heavy alcohol consumption** with sulphonylureas
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics
4. **Heavy alcohol consumption** with meglitinides (e.g. nateglinide)
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics
5. **Heavy alcohol consumption** with thiazolidinediones (e.g. pioglitazone)
Rationale: Alcohol consumption can enhance the hypoglycaemic effects of antidiabetics

Musculoskeletal and joint diseases

1. **Heavy alcohol consumption** with any nonsteroidal anti-inflammatory drugs (NSAIDs) (including COX-2 inhibitors)
Rationale: Heavy alcohol consumption and NSAID use carry an increased risk of gastrointestinal bleeds
2. **Heavy alcohol consumption** combined with methotrexate or leflunomide
Rationale: Heavy alcohol consumption combined with methotrexate or leflunomide may increase the risk of hepatotoxicity
3. **Heavy alcohol consumption** with oral muscle relaxants (e.g. baclofen)
Rationale: Concurrent alcohol consumption and muscle relaxants can increase the risk of CNS depression

Malignant disease and immunosuppression

1. **Any alcohol consumption** with procarbazine
Rationale: A disulfram-like reaction can occur when alcohol is given with procarbazine
2. **Heavy alcohol consumption** with interferon alpha or interferon beta
Rationale: Heavy alcohol consumption combined with interferons may increase the risk of hepatotoxicity and reduce the response to treatment with interferon

Infections

1. **Heavy alcohol consumption** with anti-mycobacterial medications such as isoniazid, pyrazinamide, ethionamide and rifampicin (alone or in combination)
Rationale: Alcohol combined with anti-mycobacterial medications can increase the risk of hepatotoxicity
2. **Any alcohol consumption** with cycloserine
Rationale: Alcohol consumption may increase the risk of seizures in patients taking cycloserine
3. **Any alcohol consumption** with metronidazole or tinidazole
Rationale: A disulfram-like reaction can occur when alcohol is given with metronidazole

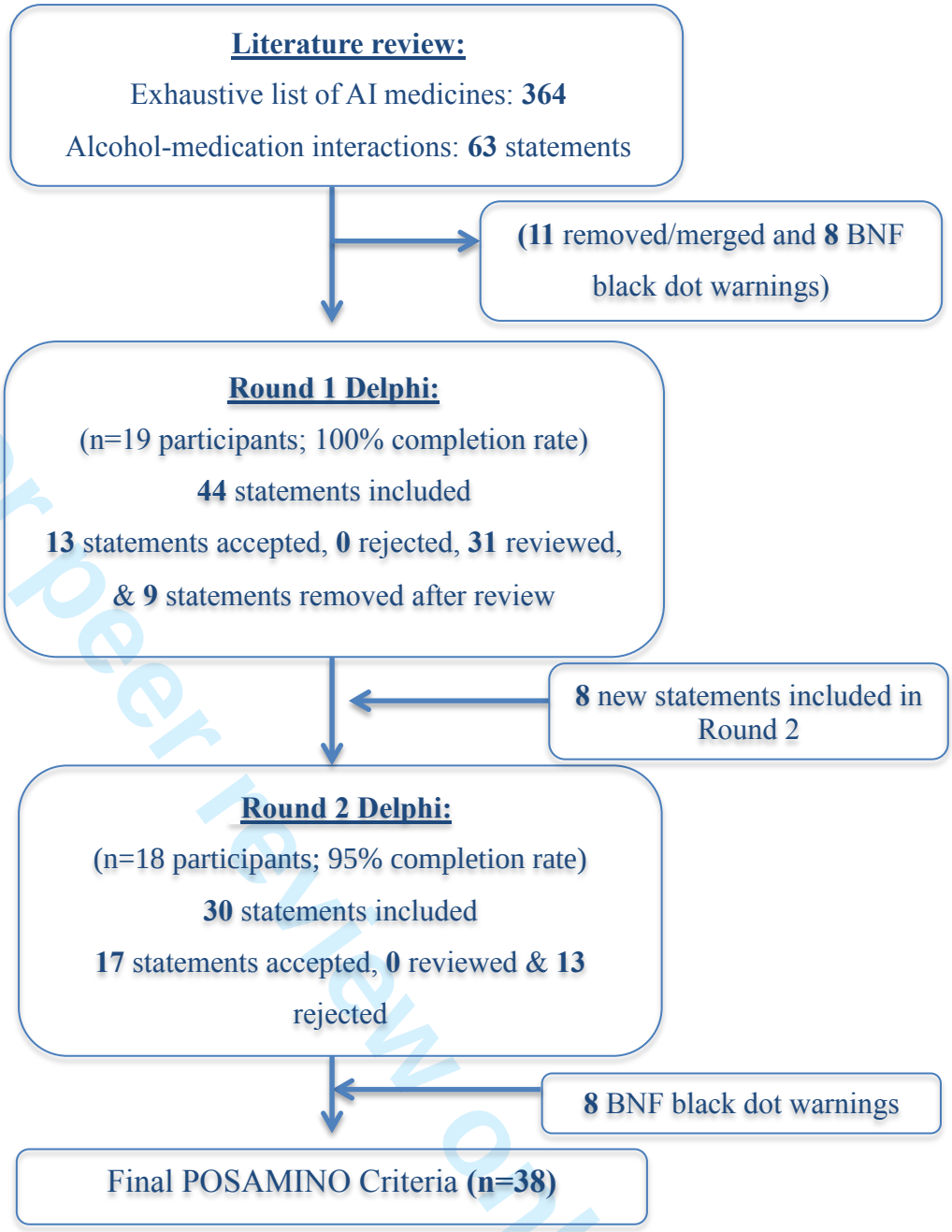

Figure 1: Flow chart summarizing the steps involved in the development of the POSAMINO criteria